Patho-physiology of anemia in CKD

By
Dr. Ahmed Mohammed Abd El Wahab
Lecturer of internal medicine
(Nephrology)

Historical background

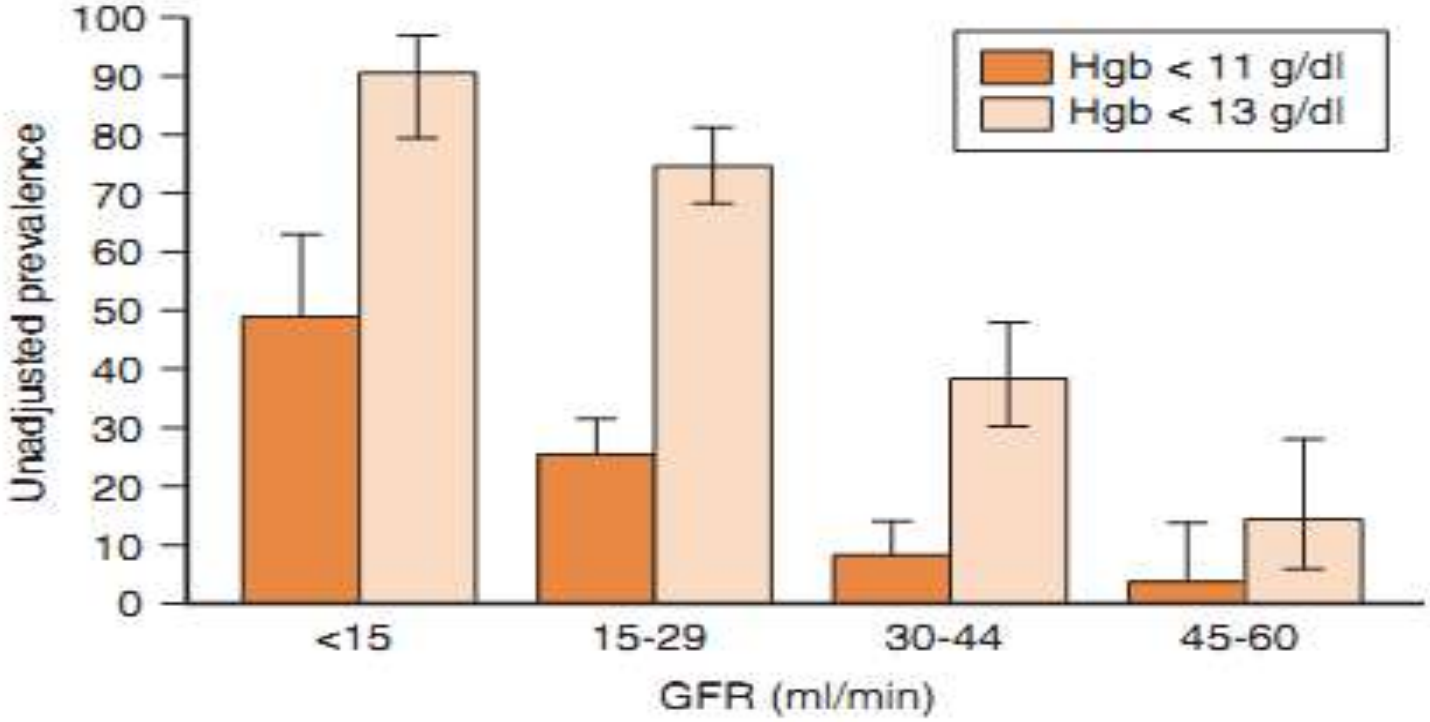
- *Richard Bright (1836):* first observed that anemia was a complication of renal failure.
- *Robert Christison*: further described renal anemia.
- *Miyake (1977):* purified and identified erythropoietin.
- *Eschbach (Dec 2, 1985):* first human use of EPO

Definition

- Anemia is a condition in which the number of RBCs or their oxygen-carrying capacity is insufficient to meet physiologic needs, which vary by age, sex, altitude, smoking, and pregnancy status (WHO).

- For diagnosis and further evaluation Hb values according to NKF guidelines:
  - <13.5 g/dL in adult males. (WHO-13g/dL)
  - <12.0 g/dL in adult females.

Prevalence (GFR)



Prevalence of anemia among untreated patients with chronic kidney disease according to degree of residual renal function. (National Kidney Foundation. *K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification.* Am. J. Kidney Dis. *2002* 39 (2 Suppl 1) S1-S266.

Prevalence (Country)

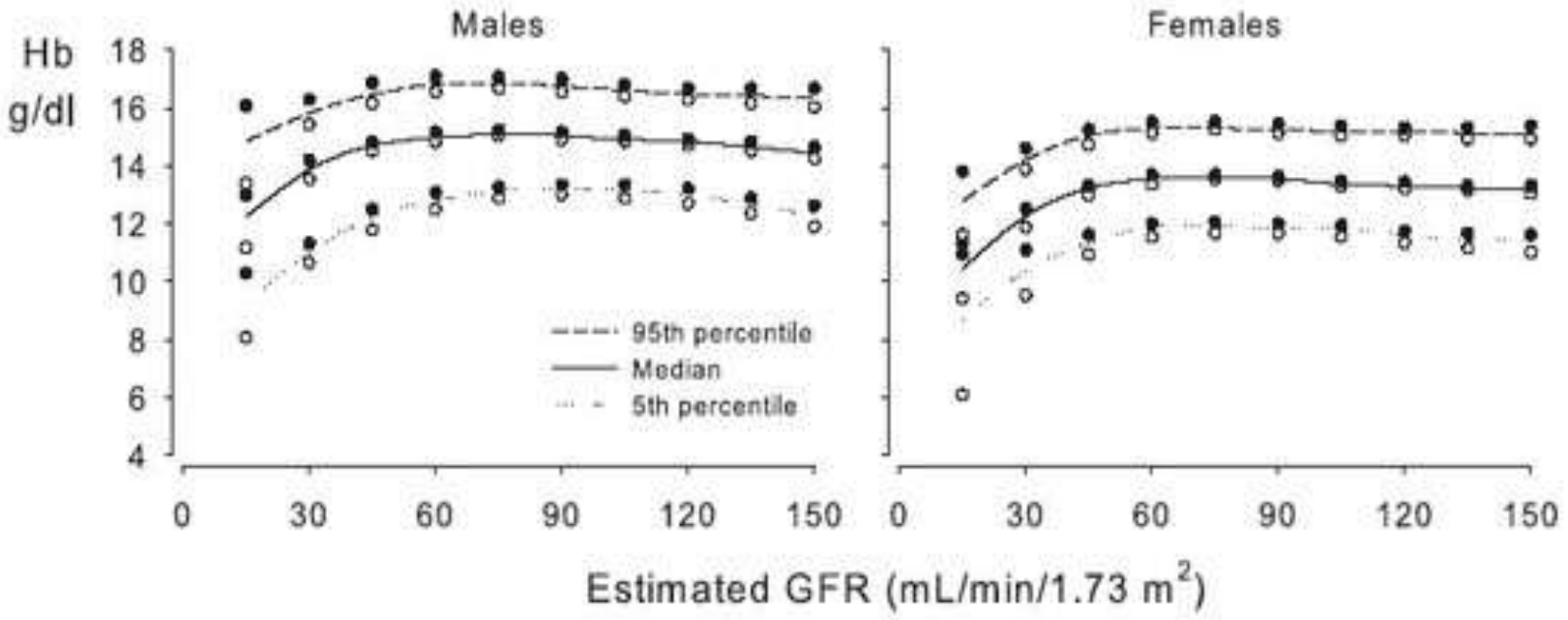
Hemoglobin Levels in Patients on Dialysis

Country	Among Patients on Dialysis for Longer Than 180 Days			Among Patients New to ESRD, at Start of Dialysis		
	n	Mean Hb (g/dl)	Hb <11 g/dl (% of patients)	n	Mean Hb (g/dl)	Hb <11 g/dl (% of patients)
Sweden	456	12.0	23	168	10.7	55
United States	1690	11.7	27	458	10.4	65
Spain	513	11.7	31	170	10.6	61
Belgium	442	11.6	29	213	10.3	66
Canada	479	11.6	29	150	10.1	70
Australia and New Zealand	423	11.5	36	108	10.1	70
Germany	459	11.4	35	142	10.5	61
Italy	447	11.3	38	167	10.2	68
United Kingdom	436	11.2	40	93	10.2	67
France	341	11.1	45	86	10.1	65
Japan	1210	10.1	77	131	8.3	95

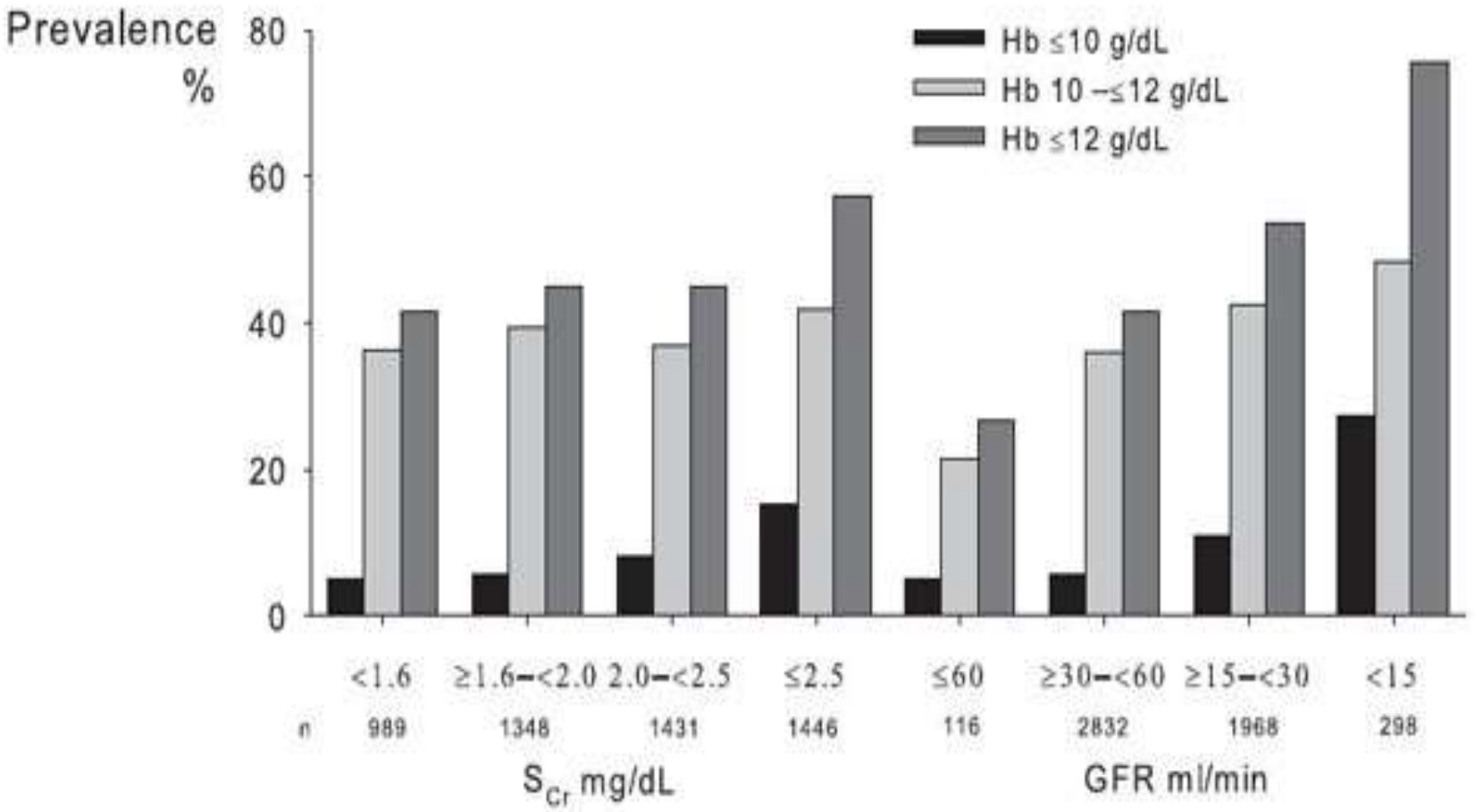
Mean hemoglobin (Hb) levels and percentage of patients with Hb levels below 11 g/dl who have been on dialysis therapy for more than 180 days and at the time of starting dialysis, by country. Data are from the Dialysis Outcomes and Practice Patterns Study, Phase II (DOPPS

Prevalence (gender)

- According to the NHANES III data, the drop in Hb was significant in males whose GFR dropped below 75ml/min and females whose GFR dropped below 45ml/min



Prevalence (S_{cr})



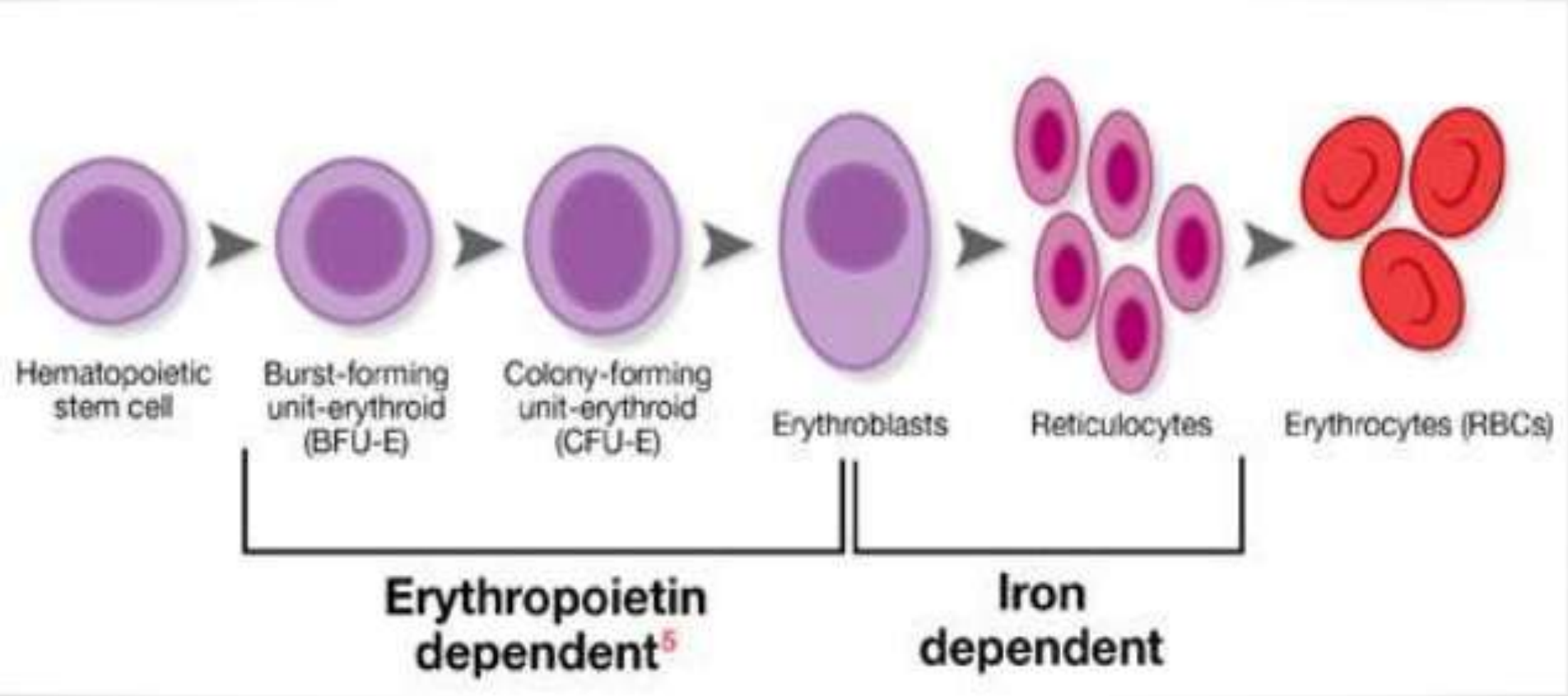
Curr Med Res Opin 20:1501-1510, 2004

Table 3. Prevalence of anemia. **(CKD stage)**

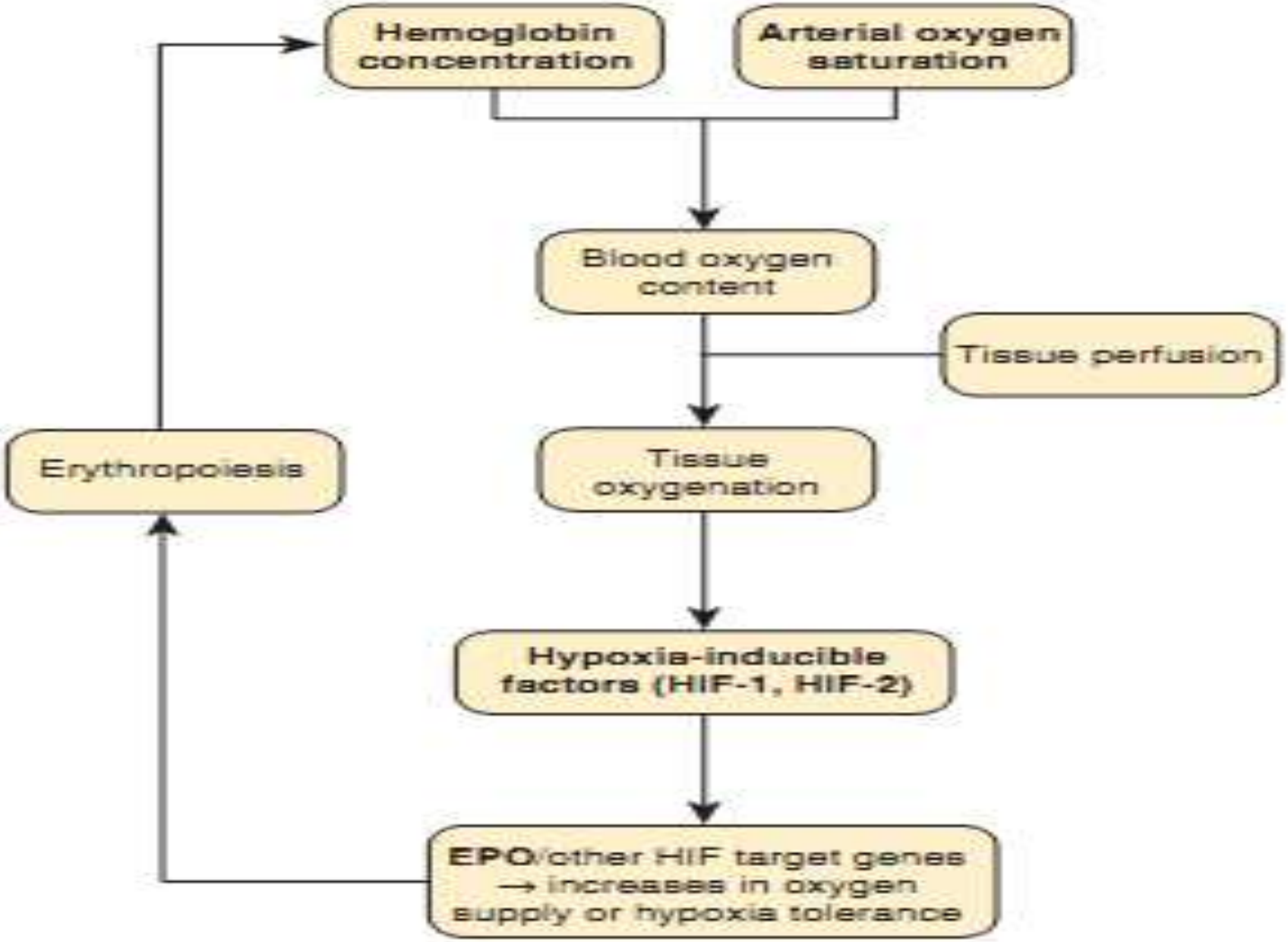
	N	Weighted percentage	95% CI	Projected number in US
With CKD	410	15.4	13.1–18.2	4.8×10^6
Stage 1	57	8.4	5.5–12.4	0.6×10^6
Stage 2	68	12.2	9.2–16.0	0.9×10^6
Stage 3	231	17.4	13.7–21.8	2.7×10^6
Stage 4	37	50.3	37.2–63.4	0.5×10^6
Stage 5	17	53.4	34.1–71.7	0.2×10^6
Without CKD	729	6.3	5.3–7.4	11×10^6

Physiology

Normal erythropoiesis



Feedback Control of Erythropoiesis



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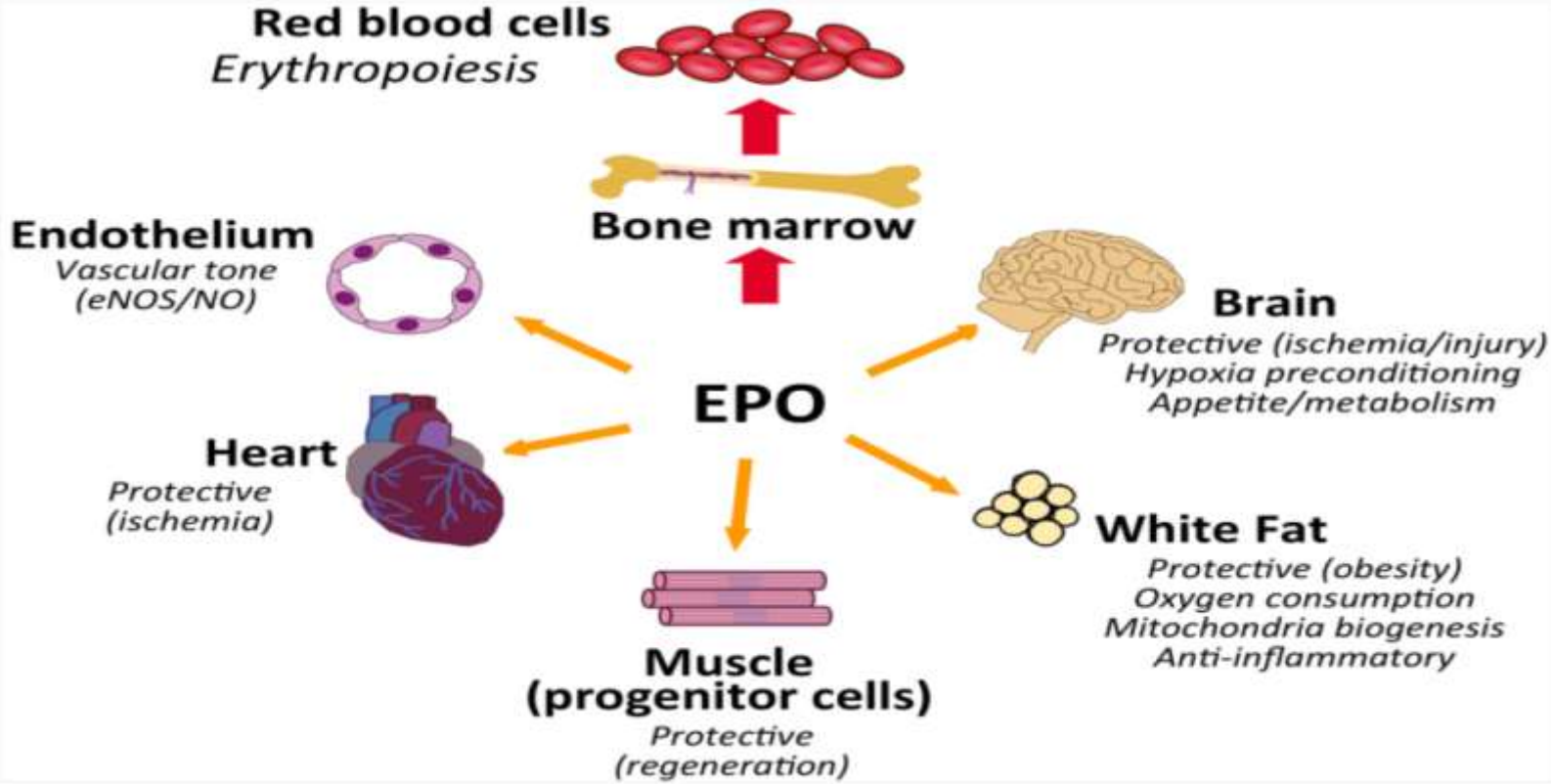
Review

Erythropoietin Action in Stress Response, Tissue Maintenance and Metabolism



Erythropoietin

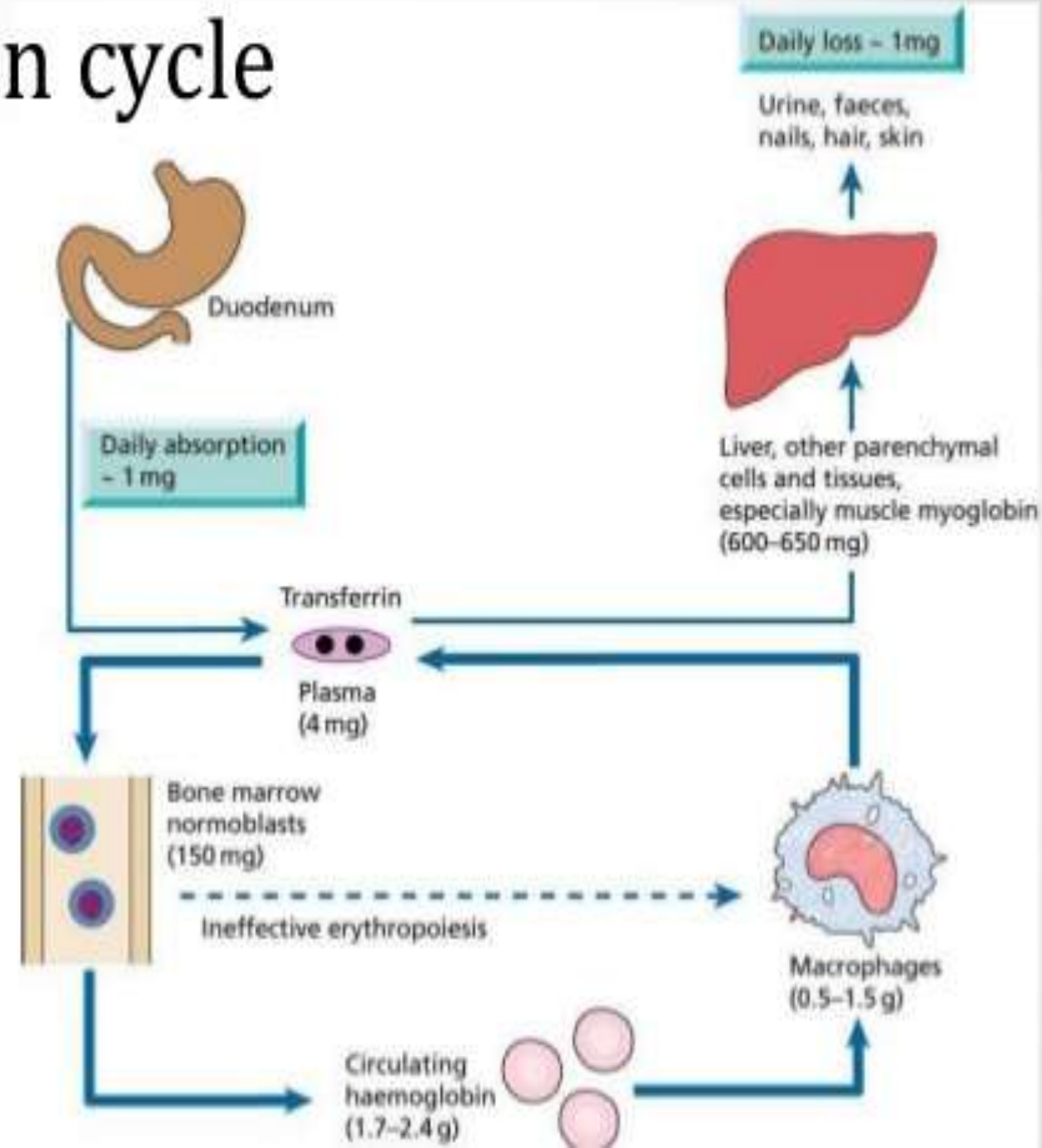
- “hemopoietine”
- 30.4 kDa glycoprotein hormone, plays a central role as a growth factor that sustains the survival of erythroid progenitor cells.
- Primary site of production is the liver in the fetus and kidneys after birth.
- Major sites of production-peritubular capillary endothelial cells and peritubular fibroblasts.

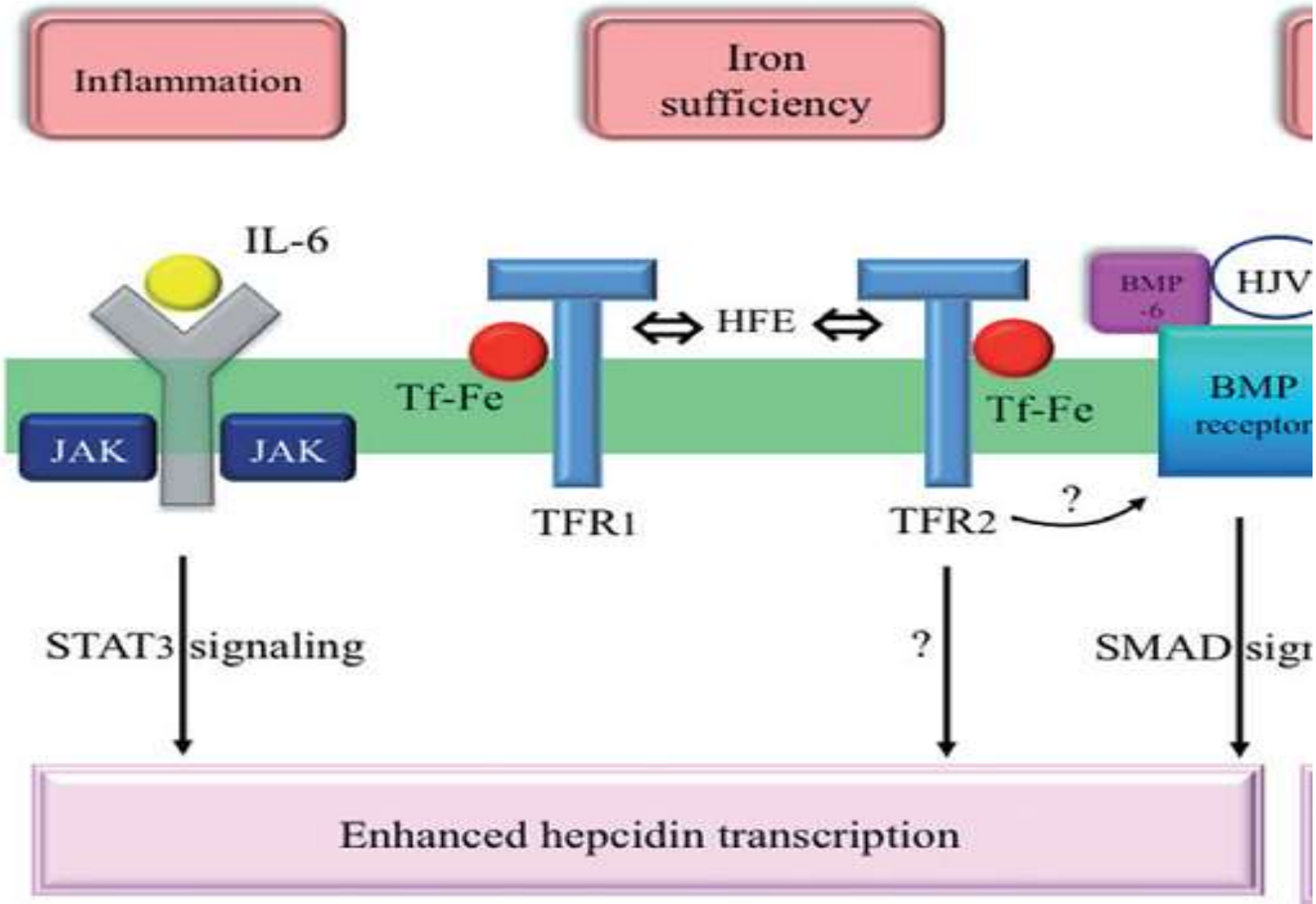
- EPO levels are considered inappropriately low relative to the degree of anemia in CKD pt.

- Similarly anemic patients with normal kidney function have 10–100 times higher EPO levels

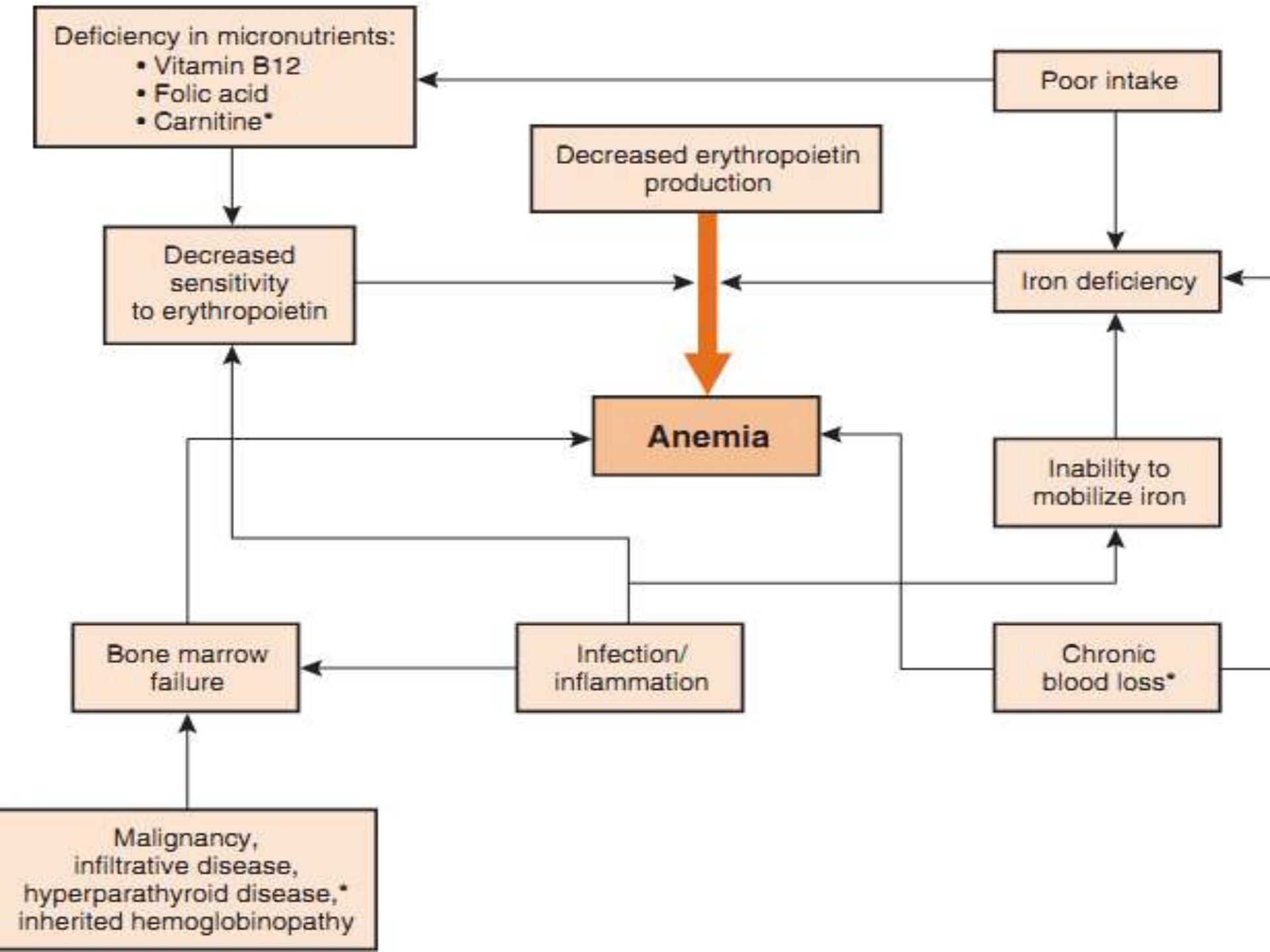
J Am Soc Nephrol 23: 1631–1634, 2012

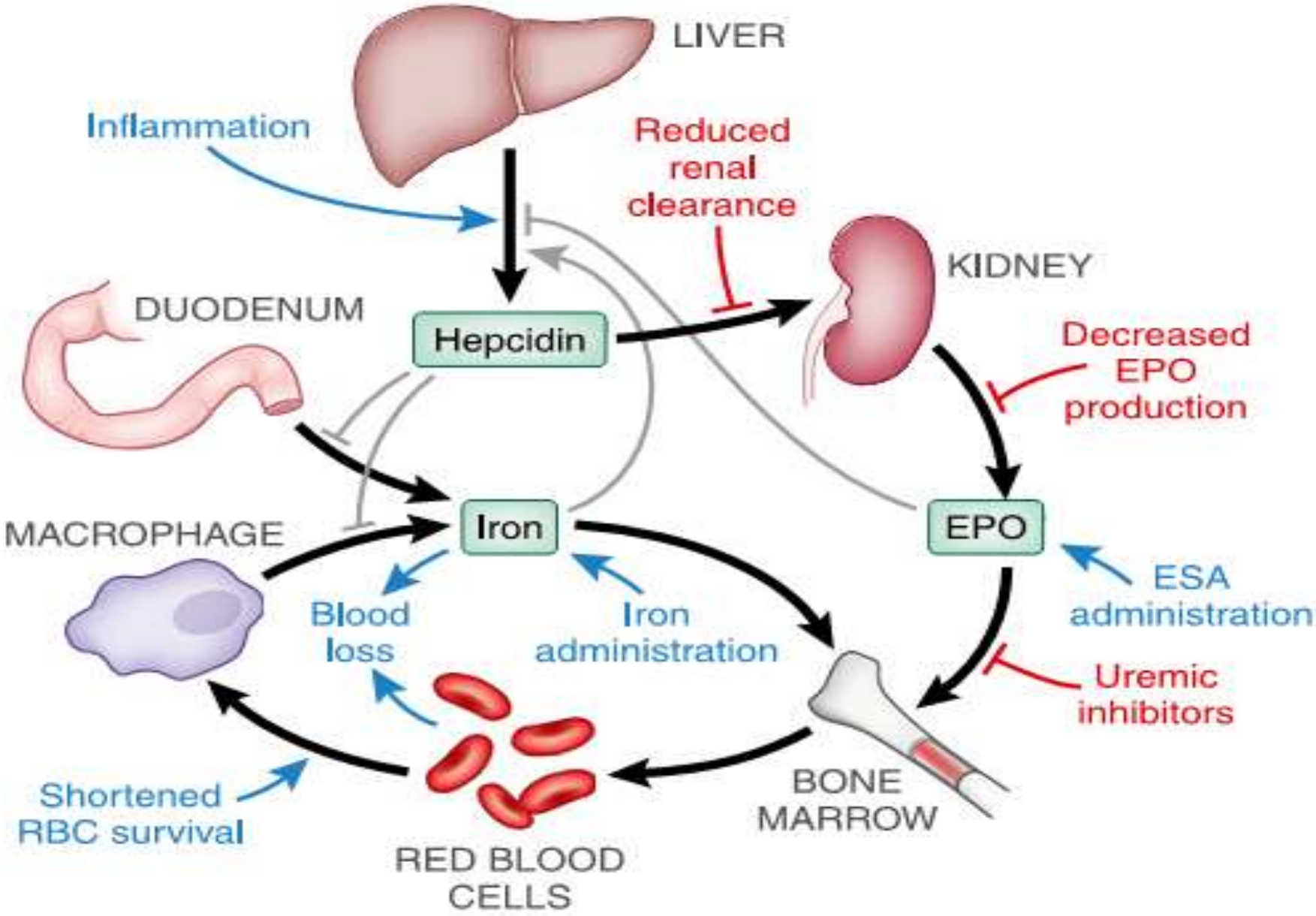
Normal Iron cycle




Inflammation
Iron sufficiency
IL-6
JAK
JAK
Tf-Fe
HFE
Tf-Fe
BMP -6
HJV
BMP receptor
TFR1
TFR2
?
STAT3 signaling
?
SMAD sign
Enhanced hepcidin transcription

Pathology


Deficiency in micronutrients:
• Vitamin B12
• Folic acid
• Carnitine*
Poor intake
Decreased erythropoietin production
Decreased sensitivity to erythropoietin
Iron deficiency
Anemia
Inability to mobilize iron
Bone marrow failure
Infection/ inflammation
Chronic blood loss*
Malignancy, infiltrative disease, hyperparathyroid disease,* inherited hemoglobinopathy



J Am Soc Nephrol **23:** 1631–1634, 2012

Therapeutic Apheresis and Dialysis 2013; 17(1):1–8
doi: 10.1111/1744-9987.12001

Review Article

Hepcidin is a Potential Regulator of Iron Status in Chronic Kidney Disease

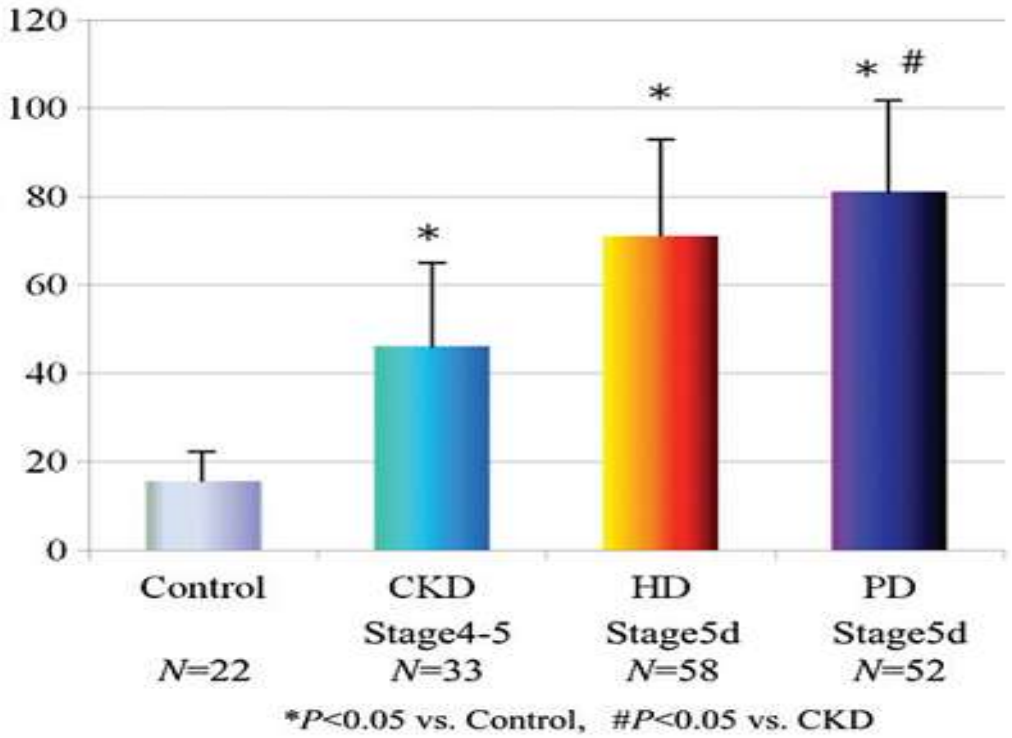


FIG. 3. Serum hepcidin-25 levels in healthy controls and chronic kidney disease (CKD) patients. The serum hepcidin-25 levels were quantified by mass spectrometry. Serum hepcidin-25 levels increased significantly as the CKD stages progressed.

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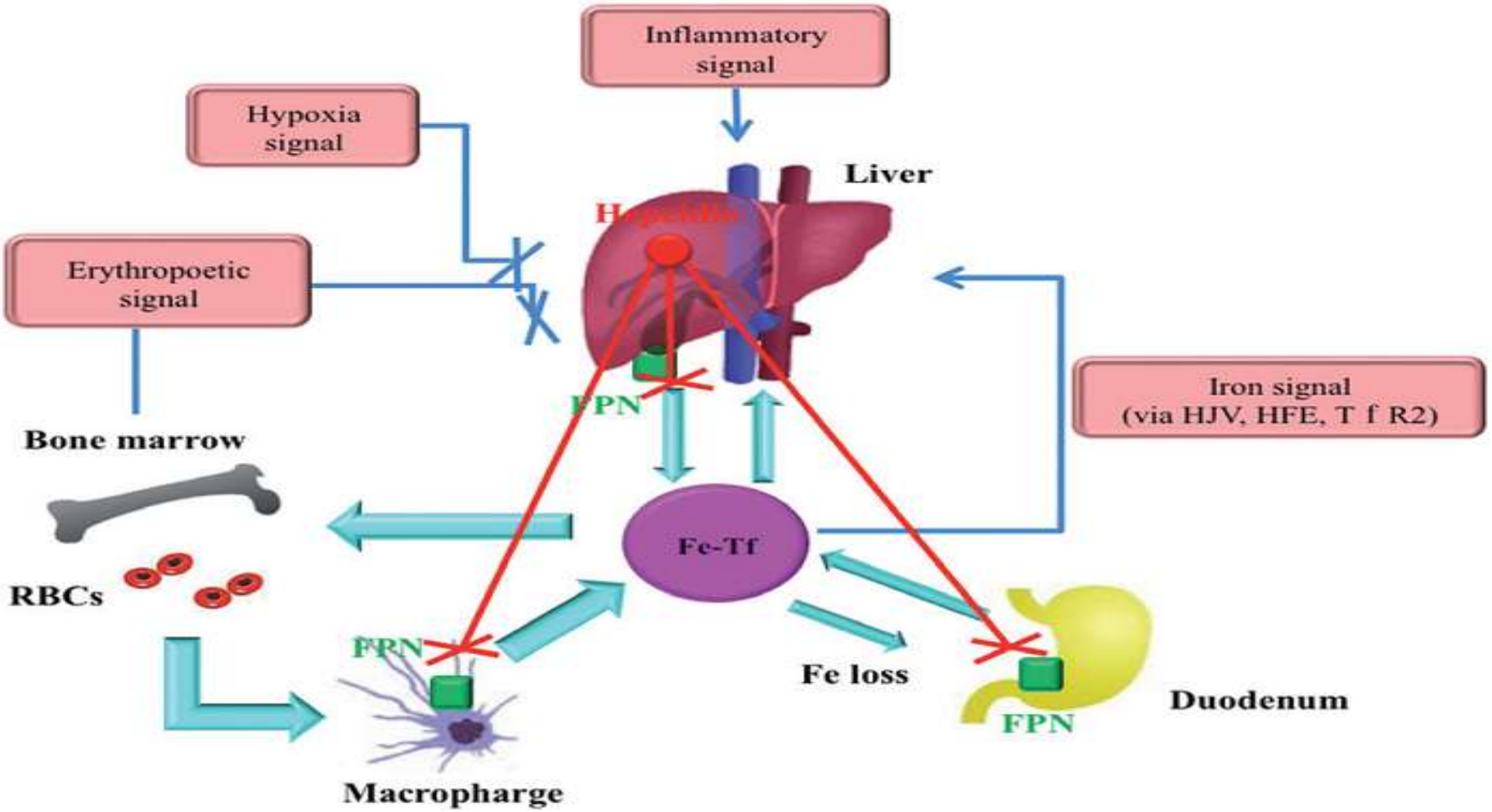

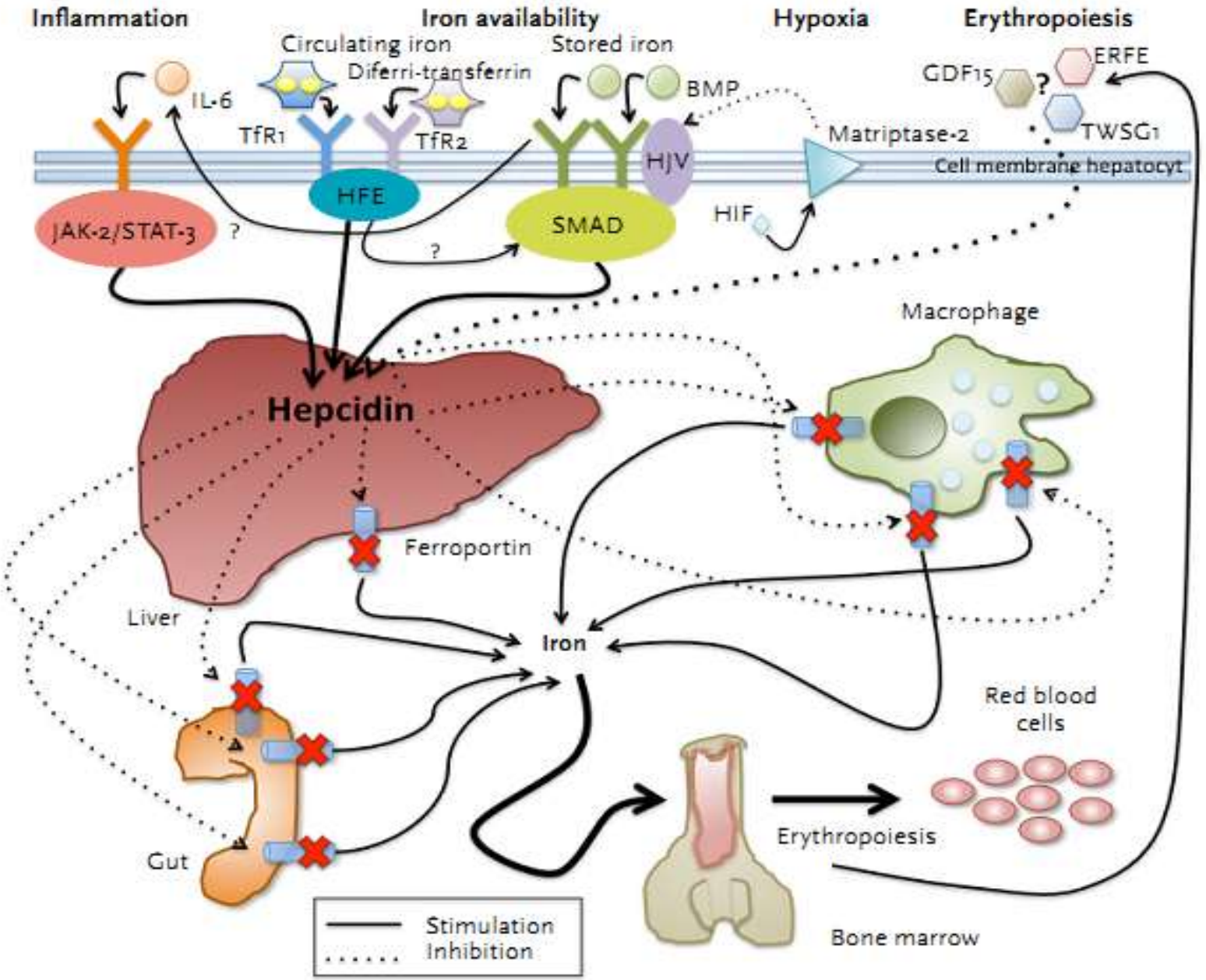
Inflammation
Iron availability
Hypoxia
Erythropoiesis
Circulating iron
Diferri-transferrin
Stored iron
IL-6
TfR1
TfR2
BMP
HJV
HFE
SMAD
JAK-2/STAT-3
?
?
HIF
Matriptase-2
GDF15
?
ERFE
TWSG1
Cell membrane hepatocyt
Macrophage
Hepcidin
Ferroportin
Liver
Iron
Red blood cells
Gut
Erythropoiesis
Bone marrow
Stimulation
Inhibition

The Netherlands Journal of Medicine

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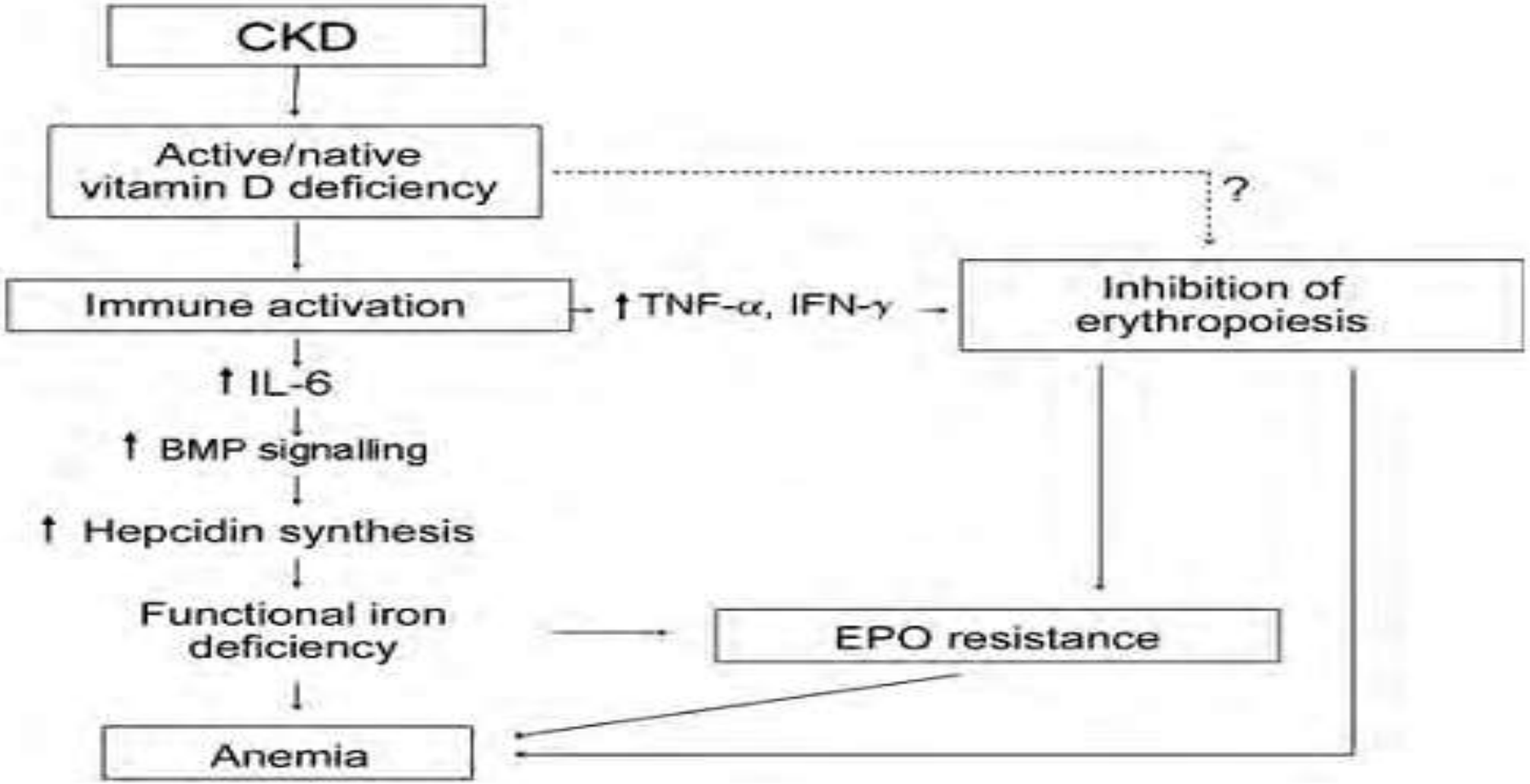
Hepcidin in chronic kidney disease: not an anaemia management tool, but promising as a cardiovascular biomarker

N.C. van der Weerd*[1], M.P.C. Grooteman[2], M.J. Nubé[2], P.M. ter Wee[2], D.W. Swinkels[3], C.A.J.M. Gaillard[4]

Nephrol Dial Transplant (2013) 28: 1672–1679
doi: 10.1093/ndt/gft021
Advance Access publication 6 March 2013

Renal anaemia and EPO hyporesponsiveness associated with vitamin D deficiency: the potential role of inflammation



Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015 Jun; 159(2):197-202.

Pathophysiology of anemia in chronic kidney diseases: A review

Josef Zadrazil, Pavel Horak

- ACEIs, ARBs:

1. Eff. A. VD------→ ↑ peritub. O_2 (site of EPO sec.)
2. ↓ IGF-1
3. ↑ apoptosis of erythroid progenitor cells

- Immunosuppression:

1. Antiprolif. eg. MMF, AZA
2. HUS, hemolysis eg. CsA, mTOR inhibit
3. BM toxicity eg. ATG

Kidney Res Clin Pract 34 (2015) 60–63

Kidney Research and Clinical Practice

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Case Report

Idiopathic erythrocytosis in a patient on chronic hemodialysis

Dong Hyun Lee, Ji Hye Min, Sang Byung Bae, Hyo Wook Gil, Jong Oh Yang, Eun Young Lee*, Sae Yong Hong

Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Cheonan, Korea

THANK YOU